REMARKS/ARGUMENTS

With this amendment, claims 23 and 36-44 are pending. Claims 1-22 and 24-35 are cancelled. For convenience, the Examiner's rejections are addressed in the order presented in an April 2, 2007, Office Action.

I. Status of the claims

Claim 23 is amended to recite identification of a compound that induces cell cycle arrest. Support for this amendment is found throughout the specification, for example at page 16, line 31 through page 17, line 2; page 55, lines 16-20; and Figure 20. Claim 23 is amended to recite that the inhibition of a FANCA protein in a cell causes cell cycle arrest. Support for this amendment is found throughout the specification, for example at Figure 20. Claim 23 is amended to recite that the assay of a compound for cell cycle inhibition effect is compared to a control sample that does not include the tested compound. Support for this amendment is found throughout the specification, for example at page 16, lines 18-31. Claim 44 is amended to recite that the FANCA polypeptide "consists essentially of SEQ ID NO:6." These amendments add no new matter.

II. Objections to the claims

Claim 23 is objected for a typographical error. In order to expedite prosecution, the word "protein" has been deleted from claim 23.

III. Rejections under 35 U.S.C. §112, second paragraph

Claims 23 and dependent claims 36-44 are rejected as allegedly indefinite. First, claim 23 is rejected as incomplete for as allegedly unclear in the relationship between modulation of the cell cycle by a compound and determining the chemical or physical effect of the compound on a FANCA polypeptide. In order to expedite prosecution, claim 23 is now amended to recite that inhibition of the FANCA polypeptide results in inhibition of the cell cycle. Claim 23 is also rejected for recitation of "modulation of the cell cycle". In order to

expedite prosecution, claim 23 is now amended to recite "induces cell cycle arrest". Claims 36-44 is also rejected for recitation of the phrase "chemical or phenotypic effect". Claims 36-44 are now amended to delete that phrase. In view of these amendments, withdrawal of the rejection for alleged indefiniteness is respectfully requested.

IV. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 23 and 36-44 are rejected for alleged lack of enablement. According to the Office Action, the claims are enabled for the use of a FANCA polypeptide comprising SEQ ID NO:6, but are allegedly not enabled for use of FANCA polypeptides that comprise amino acid sequences with 95% identity to SEQ ID NO:6. In discussion of the FANCA protein, the Office Action also alleges that little is known about that protein. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention. *See, e.g., Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982). Moreover, "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

As set forth in the Manual of Patent Examining Procedure (MPEP) § 2164.01, "the test of enablement is not whether any experimentation is necessary, but whether… it is undue." Further, the "fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation" (citations omitted). Finally, claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid

inoperative embodiments. *See, e.g., In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971).

The amended claims are directed to methods of identifying compounds that increase cell cycle arrest using FANCA proteins with 95% identity to SEQ ID NO:6, wherein down regulation of the FANCA protein results in cell cycle arrest. The specification provides ample support for these claims. For example, SEQ ID NO:6 is provided, and, to identify proteins with 95% identity to SEQ ID NO:6, well-known sequence analysis algorithms are disclosed at, *e.g.*, page 24, lines 7-22.

The Office Action also cites a number of references that allegedly demonstrate that even minor modifications of the FANCA protein sequence would result in unpredictable disruption of protein function. Enablement is determined at the time of filing and the earliest priority date for the application is April 15, 2002. Each of the references cited by the Office Action to support the enablement rejection is more than 15 years old.

Applicants assert that those of skill had access to information on the structure and function of the FANCA protein that would allow those of skill to make and use the genus of FANCA proteins with 95% identity to the reference sequence. First the specification does provide data to demonstrate that a compound that affects the FANCA protein inhibits cell cycle arrest. Figure 20 discloses cell cycle inhibition of cell that express the FANCA "hit" identified in a screening assay. The screen is disclosed at page 74, line 29 through page 75, line 25. The FANCA hit is a C-terminal FANCA peptide fused to GFP that produces a cell cycle arrest phenotype when expressed in cells. Genetically, the observed phenotype is dominant negative, meaning that the fusion-peptide hit negatively affects FANCA activity. Although the Office Action alleges that the specification does not that FANCA is a member of a protein family, this is not accurate. Figure 19 discloses and identifies a number of FANCA protein domains with recognized functions, *e.g.*, an aldehyde dehydrogenase cysteine active site, an FKBP-type peptidyl-prolylcis-trans isomerase signature domain, and a peptidase S8 domain. Figure 19 also identifies the amino acid sequence of the FANCA protein hit used to identify FANCA as a target for inducing cell cycle arrest.

The Office Action cites four references that allegedly support the difficulty of predicting whether an amino modification will affect the function of a protein: Lin *et al.* (1975), Schwartz *et al.* (1987), Burgess *et al.* (1990), and Lazar *et al.* (1988). According to the Office Action Bowie, Lin *et al.* discloses that removal of a single amino acid residue substantially deceased the ability of glucagon to bind to its receptor. Lin *et al.* was published in 1975, more than 25 years before the earliest filing date. Applicants provide Davis and Granner in Goodman & Gilman's The Pharmacological Basis of Therapeutics 9th Ed. (1996) as Exhibit A to demonstrate the knowledge of glucagon structure and function at a time closer to the filing date. In 1996, the human glucagon amino acid sequence was known to be highly conserved and identical to that of many other mammals, including cattle, pigs and rats. *See, e.g.*, Davis and Granner at page 1511. In fact, the glucagon administered to humans was isolated from bovine or porcine pancreas. *Id.* at page 1512. Therefore, based on the known and highly conserved sequence and function of the glucagaon peptide, those of skill would have avoided making any modification to the amino acid sequence of that protein. The Office Action also asserted that Schwartz *et al.* demonstrated that a single amino acid change in the insulin amino acid sequence had a detrimental effect on activity of the protein. In fact, Schwartz *et al.* modified the insulin protein to mimic a naturally occurring mutation that was know to cause a genetically inherited version of hyperproinsulinemia. *See, e.g.*, Schwartz *et al.* at page 6408. Schwartz *et al.* assayed the mutant insulin protein and found that, as predicted, the change in *in vitro* activity mimicked and explained the clinical characteristics of the patients who carried the mutation. Thus, Schwartz demonstrates how routinely those of skill identify amino acids that contribute to protein function.

Similarly, Burgess *et al.* and Lazer *et al.* identify conserved amino acids in proteins and to demonstrate the ease of maintaining or diminishing protein function when modifying amino acids. Based comparison to related protein sequences, Burgess *et al.* identified a conserved lysine (Lys132) in the fibroblast growth factor (FGF) protein and predicted a functional role for Lys132. Burgess *et al.* at page 2130, left column. Burgess *et al.* changed Lys132, a basic amino acid, to glutamic acid, an acidic amino acid. Those of skill would recognize substitution of glutamic acid for lysine as a non-conservative and would predict the

disruption of FGF function observed by Burgess *et al.* Similarly, Lazar *et al.* identified two conserved amino acids in the TGF-α protein, based on comparisons to sequences of other members of the EGF-like protein family. Conserved amino acid Asp-47 tolerated some amino acid substitutions, while invariant amino acid Leu-48 did not tolerate the tested amino acid substitutions. Thus, the predictability of amino acid substitution by those of skill is also supported by the results of Burgess *et al.* and Lazar *et al.*

Finally, Applicants respectfully bring to the Examiner's attention two recent decisions by the Board of Patent Appeals and Interferences: *Ex parte Sun,* Appeal No. 2003-1993 and *Ex parte Bandman*, Appeal No. 2004-2319. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were enabled because the supporting specifications provided a single reference sequence and an assay for activity of the encoded protein. As discussed above, the specification and knowledge in the art provide the FANCA amino acid sequence and assays for the recited FANCA activity. Thus, based on these recent Board decisions, the claims are enabled.

In view of the above amendments and arguments, withdrawal of the rejection of claims 1-12, 14-19, 53, and 54 for alleged lack of enablement is respectfully requested.

V. Rejections under 35 U.S.C. §112, first paragraph, written description

Claims 23 and 36-44 are rejected for allegedly failing to meet the written description requirement. According to the Office Action the specification does not describe the genus of FANCA polypeptides used in the claimed methods. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

As currently applied, the specification does comply with US patent law for description of a nucleic acid or amino acid sequence. The Federal Circuit court of Appeals addressed the description adequate to show one of skill that the inventors were in possession of a claimed genus at the time of filing. *See, e.g., Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002). An applicant may also show that an invention is complete by

> . . . disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed

> invention . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. *Id.* at 1613.

Furthermore, "description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces." *See, e.g.*, 66 Fed. Reg. 1099, 1106 (2001).

The specification does provide descriptive support for the full scope of the claimed invention by providing both SEQ ID NO:6, a reference sequence for the recited polypeptides, and assays for regulation and inhibition of the cell cycle. FANCA protein activity was well-known at the time of filing, as were assays for inhibition of the cell cycle, *e.g.*, measurement of cell cycle arrest. The assays are described throughout the specification, for example, the cell cycle screen is disclosed at page 74, line 29 through page 75, line 25. This information is more than adequate to meet the written description requirement, particularly in view of *Enzo*, cited above, recent Board decisions, and the interpretation of the Written Description Guidelines evidenced by the USPTO's own Synopsis of Application of Written Description Guidelines.

Applicants again bring to the Examiner's attention the *Sun* and *Bandman* decisions by the Board of Patent Appeals and Interferences. In both cases, the board found that claims directed to sequences with 80% or 95% identity to a reference sequence were described because the supporting specifications provided a single reference sequence, teachings of areas of the claimed sequences that could be modified, and a functional assay for activity of the encoded proteins. Such teachings are included in the present application, as indicated above.

Applicants also direct the Examiner's attention to Example 14 of the Synopsis of Application of Written Description Guidelines, which analyzes a claim directed to a protein with an amino acid sequence at least 95% identical to a reference sequence, SEQ ID NO:3, and that has a catalytic activity. In Example 14, the specification provided one example of a protein that was a member of the claimed genus. The Patent Office concluded that the claim of 95% identity to a reference sequence with a specified catalytic activity was adequately described within the

meaning of 35 U.S.C. §112, first paragraph. First, the Synopsis reasons that the genus of proteins that must be variants of the claimed SEQ ID NO:3 does **not** have substantial variation since all of the members must have 95% identity to the reference sequence and must have the specified catalytic activity. Therefore, according to the Synopsis, the "single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay. . . " that could be used to identify members of the claimed genus. As described above, the specification discloses the cell cycle inhibition by the recited FANCA proteins and assays for its measurement. Thus, at a minimum, on the basis of the Synopsis of Application of Written Description Guidelines issued by the USPTO, the present claims that recite 95% identity to SEQ ID NO:6 meet the written description requirement.

In view of the above arguments and amendments, withdrawal of the rejection for alleged lack of written description is respectfully requested.

VI. Rejections under 35 U.S.C. §102

Claim 23 is rejected for alleged anticipation by two references. To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found…in a single prior art reference." *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

The claimed invention is a method for identifying a compound that induces cell cycle arrest, by contacting the compound with a (FANCA)-polypeptide that, if inhibited in a host cells is known to cause cell cycle arrest. A control assay without the compound is also performed and used by comparison to identify the compound that increases cell cycle arrest.

In order to anticipate, the cited references must contain every element of the claims at issue. The cited references do not.

A. Folias et al.

Claim 23 is rejected under 35 U.S.C. §102(a) as allegedly anticipated by Folias *et al. Human Mol. Gen.* (2002). According to the Office Action, ligand binding is a physical effect as defined in the specification and Folias *et al.* teaches that contacting the FANCA polypeptide with BRCA1 results in ligand binding and therefore, the reference allegedly teaches the steps of the claimed invention. Applicants respectfully bring to the Examiner's attention that the effects defined in the specification are changes in a characteristic of a FANCA polypeptide, *e.g.*, changes in ligand or substrate binding activity. *See, e.g.*, specification at page 21, lines 1-25, and line 9-10. The changes are observed on comparison to a control assay that lacks the tested compound. Folias *et al.* does not discloses measurement of changes in a FANCA characteristics in a test assay (with compound) as compared to a control (without compound). Therefore, Folias *et al.* cannot anticipate the claims.

B. McMahon et al.

Claim 23 is rejected under 35 U.S.C. §102(b) as allegedly anticipated by McMahon *et al. J. Biol. Chem.* (1999). According to the Office Action, ligand binding is a physical effect as defined in the specification and McMahon *et al.* teaches that contacting the FANCA polypeptide with spectrin II results in ligand binding and, therefore, the reference allegedly teaches the steps of the claimed invention. As above, the effects defined in the specification are changes in a characteristic of a FANCA polypeptide, *e.g.*, changes in ligand or substrate binding activity. *See, e.g.*, specification at page 21, lines 1-25, and line 9-10. The changes are observed on comparison to a control assay that lacks the tested compound. McMahon *et al.* does not discloses measurement of changes in a FANCA characteristics in a test assay (with compound) as compared to a control (without compound). Therefore, McMahon *et al.* cannot anticipate the claims.

In view of the above amendments and remarks, withdrawal of the rejection for alleged anticipation is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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